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Health and Environmental Effects Profile for Aniline

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16. ABSTRACT

The Health and Environmental Effects Profile for aniline was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Aniline has been evaluated as a carcinogen. The human carcinogen potency factor (q_1*) for aniline is 2.6×10^{-2} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for aniline is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ANILINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BOD	Biochemical oxygen demand
BODT	Biochemical oxygen demand, theoretical
bw	Body weight
CAS	Chemical Abstracts Service
COD	Chemical oxygen demand
CS	Composite score
DNA	Deoxyribonucleic acid
DOC	Dichromate oxygen consumed
EC_{50}	Median effective concentration
GC	Gas chromatography
i.p.	Intraperitoneal
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD_{50}	Dose lethal to 50% of recipients (and all other subscripted dosage levels)
MED	Minimum effective dose
MS	Mass spectrometry
NOEC	No-observed-effect concentration
NOLC	No-observed-lethal concentration
NOS	Not otherwise specified
pK	Dissociation constant
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion

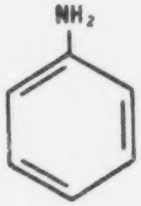
LIST OF ABBREVIATIONS (cont.)

RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
STEL	Short-term exposure level
ThOD	Theoretical oxygen demand
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as aniline is also known by the synonyms aniline oil, benzenamine, phenylamine and aminobenzene. The structure, molecular weight and empirical formula for aniline are as follows:



Molecular weight: 93.12

Empirical formula: C_6H_7N

The CAS Registry number for aniline is 62-53-3.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Aniline is a colorless oily liquid with a characteristic odor and taste (Hawley, 1981). Selected physical properties are listed below:

Melting point:	6.15°C (Northcott, 1978)
Boiling point (1 atm):	184.4°C (Northcott, 1978
Specific gravity, 20/4°C:	1.02173 (Northcott, 1978)
Refractive index, 20°C:	1.58545 (Northcott, 1978)
Vapor pressure, mm Hg:	
at 20°C	0.3 (Verschueren, 1983)
at 25°C	0.67 (U.S. EPA/NIH, 1984)
at 34.8°C	1.0 Perry and Chilton, 1973)
at 57.9°C	5.0 (Perry and Chilton, 1973)
at 25°C	0.55 (Scala and Banerjee, 1982)
pK_b at 20°C:	4.6 (Perrin, 1965)
Water solubility in ppm:	
at 20°C	34,000 (Verschueren, 1983)
at 25°C	35,000 (U.S. EPA/NIH, 1984)
at 25°C	36,600 (Kenaga, 1980)
at 18°C	36,000 (Perry and Chilton, 1973)
at 25°C	38,800 (Booth and Everson, 1949)

log K_{ow}:	0.90 (Hansch and Leo, 1979) 0.93 (Konemann et al., 1979) 0.88 (Tonogai et al., 1982) 1.09 (Eadsforth and Moser, 1983)
Nonaqueous solubility:	miscible with acetone, alcohol, benzene and ether; soluble in most organic solvents (Northcott, 1978)
Flash point (closed cup):	76°C (Northcott, 1978)
Conversion factors (air): at 20°C	1 mg/m³ = 0.259 ppm (Verschueren, 1983) 1 ppm = 3.87 mg/m³

Chemically, aniline reacts with acids to form salts and with alkaline metals to form anilides. It undergoes a variety of reactions such as C- and N-alkylation, acylation, condensation, cyclization, oxidation, reduction and diazotization, all of which have commercial importance (Northcott, 1978).

1.3. PRODUCTION DATA

The current American manufacturers of aniline are listed in Table 1-1, along with their respective locations, capacities and manufacturing processes. American Cyanamide removed itself from the aniline production market at the end of 1982 when it closed its aniline facilities at Willow Island, WV and Bound Brook, NJ (CMR, 1984).

Production volumes of aniline in recent years have been reported as follows (USITC, 1982, 1983, 1984):

Year	Production (millions of pounds)
1983	663.3
1982	557.4
1981	634.3

TABLE 1-1

United States Manufacturers of Aniline as of January, 1984*

Manufacturer	Location	Annual Capacity (millions of pounds)	Raw Material
E.I. duPont de Nemours	Beaumont, TX	260	nitrobenzene
	Gibbstown, NJ	170	nitrobenzene
First Mississippi Corp.	Pascagoula, MS	250	nitrobenzene
ICI Americas Inc. Rubican Chemical	Geismar, LA	280	ICI process
Mobay Chemical	New Martinsville, WV	42	iron oxides
United States	Haverhill, OH	200	phenol
	TOTAL	1202	

*Source: SRI, 1984

In the United States, aniline is commercially produced primarily by the catalytic reduction of nitrobenzene (Northcott, 1978). The nitrobenzene is reduced with hydrogen in a continuous vapor-phase process according to the equation:

$$C_6H_5NO_2+3H_2 \rightarrow C_6H_5NH_2+2H_2O$$

The nitrobenzene can also be reduced by the old Bechamp reduction with iron-hydrochloric acid. Mobay Chemical uses this process to produce aniline and pigment-grade iron oxide. United States Steel Corporation produces aniline from phenol as the raw material rather than nitrobenzene (SRI, 1984). Ammonolysis of phenol yields aniline (Northcott, 1978). Phenol and ammonia are passed over specialty catalysts at elevated temperatures and pressures to derive the crude aniline.

1.4. USE DATA

Aniline is used predominantly as a chemical intermediate. About 300 chemical products and intermediates are made from aniline: some are made by a single process while others, especially dyes and pharmaceuticals, require several steps (Northcott, 1978). The use patterns of aniline are given in Table 1-2. The industries consuming the major quantities of aniline are the polymer, rubber, agricultural and dye industries.

Aniline is used directly as a solvent (Kouris and Northcott, 1963) and as an anti-knock compound for gasolines (Northcott, 1978).

TABLE 1-2

Use Patterns of Aniline*

Use	Percent
MDI (p,p^1-methylene diphenyl diisocyanate) and polymeric MDI	60
Rubber chemicals	18
Hydroquinone	2
Pesticides and fibers	9
Exports	3
Pharmaceuticals	2
Dyes and pigments	3
Miscellaneous: (includes agriculture chemicals, specialty resins, and photographic chemicals)	3

*Source: CMR, 1984

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of aniline in the environment will depend upon the ability of the compound to undergo chemical, photochemical and biological reations and to transport or partition from one environmental matrix into another.

2.1. WATER

2.1.1. Hydrolysis. Sufficient data are available to suggest that aniline is not environmentally susceptible to hydrolysis (Federal Register, 1984). Lyman et al. (1982) reported that aromatic amines are generally resistant to hydrolysis. Aniline has been reported to be a hydrolysis product of acetanilide and the herbicide, fenuron (U.S. EPA/NIH, 1984).

2.1.2. Oxidation. The occurrence of chemical oxidation of organic chemicals in aquatic environments may be due to several different oxidants, such as singlet oxygen ($^1O_2$), alkyl peroxyl radical ($RO_2\cdot$), alkoxy radical ($\rightarrow RO\cdot$) or hydroxyl radical ($\cdot OH$), which are generated primarily by sunlight (Mabey et al. 1981). One oxidation reaction initiated by $RO_2\cdot$ is the following:

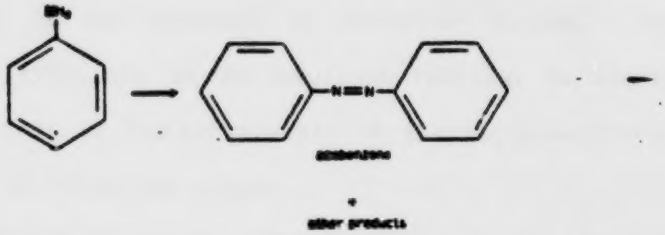
$$RO_2\cdot + ArNH_2 \rightarrow RO_2H + ArNH$$

This reaction in the aquatic environment is quite rapid, with a half-life of less than several days in sunlit water (Mabey et al., 1981). This suggests that $RO_2\cdot$ oxidation may be a significant removal mechanism for aniline in sunlit waters.

Anbar and Neta (1967) reported that the rate constant for the reaction of aniline with $\cdot OH$ at pH 9 and room temperature is 5.3×10^{9} M^{-1} sec^{-1}; assuming an aquatic $\cdot OH$ concentration of 10^{-17} M, a half-life of 151 days can be calculated. Pouyet and Chapelon (1971) reported that aniline in aqueous solution is oxidized by singlet oxygen generated at 365 nm; however, the environmental significance of this cannot be determined from the available data. Kotzias et al. (1982) noted the rapid photooxidation of aniline in water containing nitrate or nitrite. Nitrate is usually present in trace amounts only in surface waters, but occasionally occurs in high concentrations in some groundwaters (Smart and Mancy, 1984); agricultural runoff from fertilized soils may contain high nitrate levels.

2.1.3. Photolysis. The UV spectra for aniline in a cyclohexane solvent shows an absorption maxima at 287 nm with considerable absorption at >290 nm (Sadtler, 1960); in water, the absorption maxima occurs at 280 nm (Draper and Crosby, 1983a). Zepp et al. (1981) measured the photolysis of aniline (10^{-5} M) in test tubes exposed to the sunlight; a half-life of ~1 week was observed using distilled water. Kondo (1978) exposed aqueous solutions of aniline in quartz test tubes to sunlight and observed a degradation rate corresponding to a half-life of ~4 days. These tests are suggestive of photolysis in neutral waters at near-surface conditions only. Because of decreasing light intensities rates will become slower as water depths increase.

Zepp et al. (1981) also studied the photosensitized photolysis of aniline solution by humic substances found in natural waters and humic substances derived from soil. Half-lives of 4-8 hours were determined for aniline in the presence of the humic substances as compared with the 1-week half-life in distilled water only. Azobenzene and other products (not identified) were found as photolysis metabolites and are thought to result from the coupling of aniline free radicals formed by hydrogen transfer from the nitrogen of the aniline to the sensitizer; the overall reaction may be depicted as follows:



Santhanam and Ramakrishnan (1972) showed that compounds such as benzophenone and 2-acetonaphthone photosensitize the oxidation of aniline at 365 nm, while Chapelon et al. (1973) demonstrated that xanthenic dyes are aniline photosensitizers.

Zepp and Schlotzhauer (1983) examined the influence of algae on the photolysis rate of aniline in water and observed a remarkable increase in the photoreaction rate under laboratory conditions in which algae concentrations exceeded typical natural freshwater concentrations by several orders of magnitude. A photoreaction rate (for near-surface conditions) for aniline sorbed to algae was estimated to be 55 hr^{-1}; however, the authors suggested that light-induced algal transformation in typical lakes and rivers may not have a significant effect on the ambient aniline concentration present within these lakes and rivers. Algae were demonstrated, however, to be very effective photosensitizers.

Zechner et al. (1976) studied the photolysis of aniline in aqueous alkaline solution (pH 9) and acidic solution (pH 2) using UV radiation of 254 nm. In the alkaline solution, the aniline radical $C_6H_5NH\cdot$ was formed, while in acidic solution, the protonated radical $C_6H_5NH_2{+}$ and H-adduct $H\cdot C_6H_5NH_3{+}$ were formed. The photolysis end-products were identified as hydrazobenzene, 4-aminodiphenylamine and traces of 2-aminodiphenylamine, benzidine and azobenzene.

Draper and Crosby (1983a,b) demonstrated that aqueous solutions of aniline irradiated with light >283 nm photochemically produce the superoxide radical anion ($O_2^{-}\cdot$) in the presence of dissolved oxygen. The authors suggested that this anion may be an important reactant in aquatic photochemistry; however, this is another example of the photoreactivity of aniline in the presense of dissolved oxygen.

2.1.4. **Microbial Degradation.** The literature is replete with studies on the biodegradation of aniline; in most studies, aniline has been found to be significantly biodegradable. Selected data from the available literature are discussed below.

Gerlke (1984) used three different biodegradation tests with aniline and obtained the following results: Blok Test, 92% ThOD in 42 days; Closed Bottle Test, 90% ThOD in 30 days; Modified OECD Screening Test, 93% DOC removal after 28 days. Lyons et al. (1984) found that the biodegradation of aniline in pond water followed first-order kinetics, with a V_{max} of 22 μM/day. Hallas and Alexander (1983) observed that aniline completely degraded in a sewage effluent within 15 days under aerobic conditions, but did not degrade when the effluent was sterilized or used under anaerobic conditions. Brown and Laboureur (1983) reported that aniline is biodegraded >90% in 7 days using the Modified OECD Screening Test with sewage inoculum. Lammerding et al. (1982) found that Escherichia coli B converted aniline (rate constant of 0.01 hr^{-1}) to the corresponding diazonium salt. In a 5-day $^{14}CO_2$-evolution test with activated sludge, Korte and Klein (1982) reported a value of 37% CO_2, which is indicative of rapid degradation. Subba-Rao et al. (1982) examined the mineralization of ^{14}C-aniline in natural White Lake water and found, at the dilute concentrations used (54 pg/mℓ to 50 ng/mℓ), that ~80% mineralization occurred within 3 weeks.

Means and Anderson (1981) measured the biodegradability of aniline using five different tests and found aniline to be metabolized rapidly in all tests; the tests included the BOD, Shake Flask, CO_2 Evolution and Activated Sludge, as well as a test devised by Gledhill that incorporates aspects of both CO_2 evolution and shake flask tests. Cerniglia et al. (1981) determined that a strain of _Agmenellum_ _quadruplicatum_ and _Oscillatoria_ metabolized aniline to formanilide, acetanilide and p-aminophenol. Aoki et al. (1984b) reported that a species of _Frateupia_ isolated from soil rapidly biodegrades and converts it to catechol and ammonia. The catechol then degrades to CO_2 and H_2O. Using a CO_2-evolution test, Gilbert and Lee (1980) determined that aniline was readily biodegradable, as 80% of theoretical CO_2 was produced in 20 days. Calamari et al. (1980) tested the biodegradation of aniline (10-100 ppm) with river mud bacteria, sludge bacteria and adapted sludge bacteria; 100% of the aniline disappeared in 14 days with 38-83% of theoretical O_2 consumed. Schefer and Waelchli (1980) found aniline readily degradable (80-100% DOC removal) in a static test method using activated sludge. Aniline has been shown to extensively biodegrade in the Closed Bottle (BOD) Test, OECD Screening Test (Sengul and Muezzinoglu, 1980) and the Japanese MITI Test (Kawasaki, 1980).

Gerike and Fischer (1979) tested the biodegradability of aniline with the following results: Coupled Units Test, 98% DOC removal in 4 days; Zahn-Wellens Test, 100% DOC removal in 3 days; MITI Test, 99% BODT; Sturm Test, 92% CO_2 evolution, 98% DOC removal; OECD Screening Test, 93% DOC removal; Closed Bottle Test, 90% BODT in 30 days. Kitano (1978) found that aniline completely degraded in activated sludge in 2 weeks at 100 ppm concentration.

Kondo (1978) examined the biodegradation of aniline in seawater and in freshwater at 30°C in the dark and found 40-50% degradation in 1 day with little additional degradation at the end of 3 days. Baird et al. (1977) measured the depletion rate of aniline (20 ppm) in an activated sludge to be ~54% in 6 hours. Using an acclimated activated sludge, Pitter (1976) estimated a rate of biodegradation of aniline at 19.0 mg COD mg^{-1} hr^{-1} with 94.5% removal based on COD.

Using microbes isolated from raw sewage, Young et al. (1968) measured a 5-day BODT of 44% and a 20-day BODT of 64% for aniline. Malaney and McKinney (1966) found little degradation of aniline by benzene-acclimated activated sludge. Lutin et al. (1965) determined an aniline BODT of 45.7% in 144 hours using an activated sludge and the Warburg technique. Marion and Malaney (1964) found aniline to be relatively inert to biological transformation in an activated sludge for a 24-hour period, but relatively degradable during extended aeration. Chambers et al. (1963) measured an aniline BODT of 13.2% in 210 minutes using phenol-adapted bacteria.

Yoshida and Kojima (1978) identified aniline as a metabolite in the microbial degradation of diisopropylnaphthalene.

2.1.5. Transport. The transport of aniline in the aquatic environment will depend on the ability of the compound to volatilize, to adsorb to particulate organic matter and sediment in the water, and to bioaccumulate in aquatic organisms.

2.1.5.1. VOLATILIZATION -- The Henry's Law Constant for aniline at 25°C can be calculated from the water solubility (~35,000 ppm) and vapor pressure (0.55 mm Hg) to be 1.9×10^{-6} atm-m^3/mole. This value of Henry's Law Constant suggests that volatilization will occur generally at a slow rate in the environment (Lyman et al., 1982). In Erlenmeyer and Gledhill flasks, Lyons et al. (1984) measured the volatilization of aniline from pond water under aerobic conditions; volatilization appeared to follow zero-order kinetics with 0.002% of the aniline being eliminated per day, which was considerably slower than aniline loss from microbial degradation. Therefore, aniline volatilization is not expected to be significant in relation to other removal mechanisms such as microbial degradation, photolysis and oxidation.

2.1.5.2. ADSORPTION -- Means (1983) experimentally determined a K_{oc} for aniline in water containing colloidal size dissolved organic carbon. At pH 6.5, a K_{oc} value of 3870 was determined, which indicates relatively strong adsorption. This suggests that aniline adsorption to organic particulates in the aquatic environment may have some importance.

2.1.5.3. BIOACCUMULATION -- In a model aquatic ecosystem, Lu and Metcalf (1975) found that aniline (0.01-0.1 ppm) was rapidly and completely detoxified to polar metabolites by Daphnia and freshwater snails. Algae and mosquito retained no aniline, but did retain small levels of N-methyl and N,N-dimethylaniline, respectively. Fish (Gambusia) retained small amounts of unchanged aniline and other metabilites, such as N-methylaniline, N,N-dimethylaniline, acetanilide, and m-, o- and p-hydroxyaniline. The ecological magnification for the fish was determined to be 6.

Freitag et al. (1982) used static water tests to determine the BCF of aniline (50 μg/ℓ) in algae and fish (golden orfes). The 1-day BCF for aniline in algae was found to be 4, while the 3-day BCF in the fish was <10. Geyer et al. (1981) also reported a BCF of 4 for aniline in the alga Chlorella fusca.

Kenaga (1980) predicted the BCF for aniline to be 2, based on its water solubility and use of a regression formula derived by Kenaga and Goring (1978); this estimation is consistent with the experimental data above. The BCF can also be predicted from the K_{ow} by use of the equation presented by Veith et al. (1980): $\log BCF = 0.76 \log K_{ow} - 0.23$. For aniline, log K_{ow} is ~0.90, which yields a BCF of ~3.

The bioaccumulation data presented for aniline indicate that bioaccumulation in aquatic organisms is not significant.

2.2. AIR

The chemical removal processes in the atmosphere include reaction with hydroxyl radicals, reaction with other radicals, reaction with ozone, and photolytic transformations (Cupitt, 1980). Guesten et al. (1981) reported that the experimental rate constant for the reaction of OH radicals with aniline in the gas-phase at room temperature is 1.2×10^{-10} cm^3 $molecule^{-1}$ sec^{-1}; assuming an average OH radical concentration of 10^6 $molecules/cm^3$ in the atmosphere, a half-life of 1.6 hours is calculated, indicating rapid removal.

Filby and Guesten (1978) experimentally determined the rate constant for the reaction between aniline and $O(^3P)$ atoms (ground state oxygen atoms) to be 0.24×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}; assuming a typical atmospheric concentration of $O(^3P)$ atoms to be 2.5×10^4 $molecules/cm^3$ (Graedel, 1978), a half-life of 3300 days can be calculated, which has no environmental significance.

Rate constant data for the atmospheric reaction of aniline with other radicals were not located, nor was a rate constant found for its reaction with ozone. Brown et al. (1975) suggested that aniline reacts with O_3 on the same order of magnitude as does phenol, which has an estimated atmospheric half-life of ~1 day.

In laboratory studies, aniline has effectively been demonstrated to inhibit the production of photochemical smog generated by sunlight, which is due to its radical scavenging reactivity (Gitchell et al., 1974; Spicer et al., 1974; Nguyen and Phillips, 1975). This further demonstrates the rapid reactivity of aniline when exposed to the ambient atmosphere. The photochemical reactions of aniline in the atmosphere reportedly produce the following products: N-methylaniline, N,N-dimethylaniline, isomeric hydroxyanilines and phenols (MITRE Corp., 1976).

In addition to the chemical reactions discussed above, aniline also appears to be labile to direct atmospheric photolysis, although specific experimental data are not available. The UV spectra for aniline shows an absorption maximum at 287 nm, with considerable absorption at >290 nm (Sadtler, 1960). As noted in Section 2.1., Zepp et al. (1981) found that aniline photolyzed in distilled water in sunlight with a half-life of ~1 week, while Kondo (1978) determined an aqueous sunlight photolysis half-life of ~4 days. These data suggest that aniline is likely to undergo significant atmospheric photolysis, although the removal rate may not be as rapid as reaction with hydroxyl radicals. Meallier (1969) observed that aniline reacts with molecular oxygen, O_2, in the presence of UV light of 365 nm.

The physical removal processes in the atmosphere include dissolution (wet deposition), adsorption on aerosol particles and dry deposition (Cupitt, 1980). These physical removal processes are not judged to be important relative to the rapid chemical removal processes, although the dissolution half-life equation developed by Cupitt (1980) suggests that dissolution may have some significance.

2.3. SOIL

2.3.1. Microbial Degradation. Aoki et al. (1982, 1983a,b, 1984a,b) identified 20 aniline-assimilating bacteria that were isolated from soil and found that aniline was the sole source of carbon and nitrogen. Seven of the isolated strains belong to Rhodococcus erythropolis, five to Pseudomonas maltophilia and seven to diaminobutyric acid-type coryneform bacteria. The authors suggested that the metabolic pathway with R. erythropolis involved aniline conversion to catechol with release of ammonia, followed by catechol mineralization (ultimately to H_2O and CO_2) through a β-ketoadipic acid pathway. Schukat (1981) also reported aniline degradation by Rhodococcus species.

Zeyer and Kearney (1982) isolated a Pseudomonas sp. from soil and examined the degradation of aniline, as a sole carbon and nitrogen source, at 28°C under aerobic conditions; after 10 days of incubation, 44.2% of the ^{14}C-aniline had degraded to $^{14}CO_2$. Zeyer and Kearney (1983) used a silt loam soil to incubate aniline and observed that ~12% of the aniline was degraded to CO_2 in 20 days.

Rabsch and Fritsche (1977) determined that an Achromobacter sp. isolated from soil was able to completely degrade aniline as a sole carbon and nitrogen source. Bachofer et al. (1975) used a Nocardia sp. isolated from soil to convert aniline into pyrocatechol. Bordeleau and Bartha (1972) observed that aniline is susceptible to oxidation by enzymes isolated from a soil fungus, Geatricum candidum. Clark and Wright (1970) determined that aniline is rapidly degraded by Arthrobacter sp. and Achromobacter sp. while Walker and Harris (1969) found that Pseudomonas sp., isolated from soil, were able to use aniline as a sole carbon source.

Using a soil inoculum (Niagara silt loam) and a mineral salts medium, Alexander and Lustigman (1966) determined that aniline (10 ppm) was completely degraded in 4 days by the soil microflora. Tabak et al. (1964) isolated microbes from garden soil, compost, river mud and petroleum waste lagoon sediment (included Pseudomonas, Achromobacter, Flavobacterium and Xanthomonas) and used a Warburg respirometer, with 3 hours of incubation, to measure an aniline BODT of 11.1%. Moore (1949) found that in soil-enriched cultures of Proactinomyces aniline was used as a sole carbon and nitrogen source.

The available data clearly suggest that the microbial degradation of aniline in soil is likely to be environmentally significant.

2.3.2. Chemical Degradation. Pillai et al. (1982) examined the degradation of aniline in sterilized soil and noted degradation products including azobenzene, azoxybenzene, phenazine, formanilide and acetanilide. Other degradation products, which could not be unequivocally identified, included nitrobenzene and p-benzoquinone. The degradation mechanism was not determined, but was suggested to involve molecular oxygen as an oxidant with the soil acting as a catalyst. Parris (1980) found that aniline bound to humates is quite susceptible to oxidation.

2.3.3. Photolysis. Freitag et al. (1982) tested the photomineralization of aniline by absorbing ^{14}C-aniline in silica gel (100 ng/g) and then irradiating the gel with a UV lamp of wavelength 290 nm. In 17 hours of irradiation, 46.5% of the aniline was degraded to $^{14}CO_2$. The photolysis data discussed in Section 2.1.3. also suggest that aniline photolysis has environmental importance. Therefore, the photodegradation of aniline on soil surfaces is likely to occur at an environmentally significant rate.

2.3.4. Adsorption -- Leaching. Pillai et al. (1982) experimentally determined K_{oc} values for aniline in Hagerstown clay loam and Palouse silt loam to be 310 and 910, respectively. The K_{oc} values for the aniline metabolites were determined to be significantly higher, indicating that the metabolites are likely to be bound tightly to organics in soil. The K_{oc} values for aniline suggest low to medium soil mobility.

Moreale and Van Bladel (1976) used 14 different soil types to demonstrate that aniline adsorption increases with increasing organic content and decreases with soil pH. Mueller-Wegener (1982) used five soil types to determine similar results with respect to organic content.

Kenaga (1980) predicted the K_{oc} value of aniline, based on its water solubility to be 13 by use of a regression equation developed by Kenaga and Goring (1978). The K_{oc} can also be predicted from K_{ow} values by use of the Kenaga and Goring (1978) equation: $\log K_{oc} = 0.544 \log K_{ow} + 1.377$; for aniline, the K_{oc} value is calculated to be 96. Prediction of K_{oc} by the molecular topology and structure-activity relationship analysis of Sabljic (1984) yields a K_{oc} value of 207.

2.3.5. Volatilization. Experimental data regarding the significance of aniline volatilization from soil were not located.

2.3.6. Persistence. Thompson (1969) reported that aniline degrades readily in soil (loam) with a half-life of <1 week. Suess et al. (1978) examined the mineralization of aniline in four soil types; during 10 weeks of testing, 16.2-26.3% of the initial aniline (1 ppm) was mineralized. Mineralization is conversion to inorganic compounds, such as CO_2, and requires longer periods of time than coversion to organic metabolites. In a model soil ecosystem study, Figge et al. (1983) determined that aniline had a decay rate constant of 0.17 $days^{-1}$; this translates to a half-life of 4 days, which is consistent with the data reported by Thompson (1969).

2.4. SUMMARY

In a typical ambient environment of 25°C, aniline appears to be rapidly degraded by chemical transformations in water, air and soil matrices. In the aquatic environment, radical oxidation and photolysis (both direct and photosensitized) are potentially significant removal mechanisms. In addition, aniline has been shown to be quite readily biodegradable. Adsorption to organic particulates in the natural water may affect the persistence of aniline in water. Aniline is not expected to bioaccumulate significantly in aquatic organisms.

In the atmosphere, aniline has been shown to react very rapidly with hydroxyl radicals, with a half-life of <1 day in a typical atmosphere. Also, direct photolysis and, perhaps, reaction with ozone are potentially rapid removal mechanisms.

The available persistence data for aniline in soil indicate a half-life of <1 week. Apparently, aniline degradation in soil is accomplished primarily by microbial decomposition, but significant soil-catalyzed oxidation may also occur. Aniline is likely to photolyze quite rapidly on soil surfaces. As the organic content of soil increases, the adsorption of aniline increases; in soils of high organic content, aniline will likely have a low mobility, but in soils of low organic content, leaching is likely to occur at a moderate to high rate.

3. EXPOSURE

3.1. WATER

Aniline has been identified in the United States at unspecified levels in surface water, finished drinking water and river water, as well as in industrial effluents from chemical factories, oil refineries and coal conversion plants (Shackelford and Keith, 1976; Hushon et al., 1980). Nelson and Hites (1980) found aniline (5 ppm) in soil alongside the Buffalo River in New York, but not in the river sediment. Riggin et al. (1983) measured aniline levels of 5.2-13 ppb in chemical manufacturing wastewaters and in water from public treatment works from unspecified sources in the United States. Aniline concentrations of 705 ppb have been detected in shallow groundwater, contaminated by coal-tar waste, in Minnesota (Pereira et al., 1983). Concentrations of 0-36 ppb have been detected in Wyoming groundwater near an underground coal gasification site (Stuermer et al., 1982). Francis et al. (1980) identified aniline (no concentration given) in trench leachates collected from commercially operated low level radioactive waste disposal sites at Maxey Flats, KY and West Valley, NY. Jungclaus et al. (1978) detected aniline (0.02 ppm) in the wastewater from a specialty chemicals manufacturing plant located along the Brackish River, but not in the river water or its sediment.

Neurath et al. (1977) identified aniline (0.5-3.7 μg/kg) in three of nine surface water samples in Germany. Wegman and DeKorte (1981) found average aniline concentrations of 0.62-2.97 ppb in Rhine and Meuse River water in the Netherlands. Meijers and Van der Leer (1976) also identified aniline in Netherlands Rhine River water. Zoeteman et al. (1980) detected aniline levels of 2.3 ppb in Rhine River water before bank infiltration purification and 1.4 ppb after infiltration; similar results have been reported for West German Rhine River water (Kussmaul, 1978).

The gross analysis from the U.S. EPA STORET data base contains 128 observations for aniline, with a mean concentration of 130 μg/ℓ and minimum and maximum concentrations of 0.08 and 2800 μg/ℓ, respectively.

Exposure to aniline in the environment can result from the degradation of other chemicals, such as pesticides (Pillai et al. 1982). For example, in a model ecosystem used to study the degradation of nitrobenzene, Lu and Metcalf (1975) found aniline to be a major metabolite.

3.2. FOOD

Neurath et al. (1977) detected aniline, using GC analyses, in various food products in Germany; foods were either purchased in retail stores or freshly harvested. The concentrations detected in some food products are shown in Table 3-1. Aniline has also been found as a volatile component of black tea (Vitzthum et al., 1975).

3.3. INHALATION

York Research Corp. (1979) used GC/MS analyses to identify aniline (concentration not reported) as 1 of 53 organic compounds emitted from a coke quench tower located at the Lorain Works of U.S. Steel Corp. in Lorain, OH. Hawthorne and Sievers (1984) detected the emission of aniline to the air from shale oil wastewater; estimated concentrations of aniline in indoor air and outdoor air at the wastewater facility were 33 and 5 μg/m^3, respectively. Brodzinsky and Singh (1982) reported the detection of aniline at 9000 ppt in the urban air of Raleigh, NC during 1977 monitoring; however, it was noted that the analytical procedures used resulted in questionable quality of the data.

Graedel (1978) reported that the atmospheric emission sources of aniline include industrial sources, plastics combustion and smoke generated from

TABLE 3-1

Concentrations of Aniline in Food Products*

Food	Concentration (mg/kg)
Corn, grains	0.6
Green salad	0.6
Rhubarb	5
Apples (flesh)	1.5
Apples (peeled)	1.7
Beans (preserved)	<0.7
Bean salad	0.1
Rapeseed cake (animal feed)	120

*Source: Neurath et al., 1977

tobacco. Concentrations found in tobacco smoke range from 50.6-577 ng aniline per cigarette (Patrianakos and Hoffman, 1979). Cheeseman et al. (1980) used a biological assay method to tentatively identify aniline as a pollutant emission from a chemical plant (using aniline as an intermediate) in North Carolina.

3.4. DERMAL

Pertinent data regarding dermal monitoring of aniline were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

The ability of aniline to induce systemic toxic effects after oral, dermal and inhalation exposure is indirect evidence of absorption from the routes of exposure.

Quantitative data on the rates of aniline absorption are available only for dermal exposures. In a study by Baranowska-Dutkiewicz (1982), 10 healthy volunteers were exposed to aniline by immersion of a hand in aqueous solutions of 1 or 2% aniline for periods of 30 or 60 minutes. The amount of aniline absorbed was calculated by measuring the amount of p-aminophenol excreted in the urine over a 24-hour period. Absorption rates ranged from 0.15-1.38 mg/cm^2/hour depending upon the concentration and duration of exposure. About four times as much aniline was absorbed from the 2% solution as from the 1% solution. The apparent absorption rate of aniline tended to decrease with time, probably reflecting a first order rather than zero order absorption process. In another set of experiments, 0.25 mℓ of liquid aniline or aniline with 3% water was placed under a watch glass directly on the forearm of subjects. Absorption rates varied from 1.8-4.6 mg/cm^2/hour, with no significant differences noted between liquid aniline and aniline with 3% water.

As summarized in ACGIH (1980), a Polish study by Dutkiewicz (1962) reported that the rates of absorption across the skin and lungs are approximately equal during exposure to aniline vapor. IARC (1982) summarized several additional studies from the Polish literature (Dutkiewicz, 1961; Dutkiewicz and Piotrowski, 1961; Piotrowski, 1957, 1972) indicating that aniline absorption on dermal or inhalation exposures can be quantified by the measurement of urinary p-aminophenol.

4.2. DISTRIBUTION

Male Fischer 344 rats were injected with 3, 30 or 100 mg/kg bw of ^{14}C-aniline hydrochloride and were killed 0.5, 6 or 24 hours after dosing (Irons et al., 1980). Autoradiography on sagital sections of the entire rat, which had been frozen in liquid nitrogen under sodium pentobarbital anesthesia, revealed that the highest levels of radioactivity 0.5 and 6 hours after dosing were associated with the blood, liver, kidney, bladder and gastrointestinal tract. Although there was a time-dependent decrease in radioactivity in all organs at the two lower dose levels of ^{14}C-aniline hydrochloride, the ^{14}C-aniline-associated radioactivity persisted at a constant level from 0.5-24 hours after dosing in the red pulp of the spleen in rats injected with 100 mg/kg bw of ^{14}C-aniline hydrochloride.

Bus et al. (1978) found that plasma radioactivity peaked 0.5, 1.0 and 2.0 hours after rats were gavaged by 10, 30 and 100 mg/kg of ^{14}C-aniline hydrochloride, respectively. Although radioactivity was reported in all tissues, the highest levels occurred in the kidney, liver, plasma, lung, heart, spleen and brain. Distribution of the radioactivity was not affected by the dose levels administered (Bus et al. 1978).

4.3. METABOLISM

Booth and Boyland (1957) reported that the major route of aniline metabolism was ring hydroxylation to form aminophenols. N-hydroxylation was reported in the perfused cat liver (Kiese and Uehleke, 1961) and by hepatic microsomal preparations from several species _in vitro_ (Kiese, 1966). As reviewed by IARC (1982), Kiese (1966) reported that nitrosobenzene and phenylhydroxylamine appeared in the blood of dogs and cats after aniline administration by an unspecified route. Both phenylhydroxylamine and the aminophenols have been reported to cause methemoglobin (Harrison and Jollow, 1981), although phenylhydroxylamine may be the more potent cause of methemoglobin formation (IARC, 1974, 1982).

Examination of the contents and mucosa of the stomach and jejunum of rats 0.5 hours after they were intravenously injected with 100 mg/kg ^{14}C-aniline hydrochloride revealed that aniline was the predominant radioactive component of the gastric contents, but acetanilide was the predominant radioactive component of the small intestinal contents (Irons et al., 1980). Small amounts of 2-aminophenol and 4-aminophenol, as well as trace amounts of acetaminophen, were present in both the stomach and small intestine. Irons et al. (1980) postulated that the gastrointestinal mucosa was the principal site of the metabolism of aniline to acetanilide in rats. Although aniline was concentrated in the gastric contents, both aniline and its metabolite, acetanilide, were absorbed in the small intestine and no significant amounts of radioactivity were found in the feces (Irons et al., 1980).

When radioactive ^{14}C-aniline was added to the perfusion medium for 3 hours in perfused rat livers, most of the radioactivity was recovered as an acid-labile complex in the perfusate. In addition, free aniline, other stable aniline conjugates and 4-aminophenol conjugates were identified. No free 4-aminophenol was reported in the perfusate (Boobis and Powis, 1975).

As summarized by NRC (1983), aniline is first oxidized by hydroxylation of a ring carbon to form 2- or 4-aminophenol or by hydroxylation of the nitrogen to form phenylhydroxylamine and then conjugated to glucuronic or sulfuric acid. Formation of mercapturic acid conjugates may occur after phenylhydroxylamine has reacted with cysteine (Boyland et al., 1963). The urine of all species treated with aniline contained 4-aminophenol as a glucuronic acid or sulfate conjugate (Gut and Becker, 1975; Williams, 1959), and measurement of the amount of urinary 4-aminophenol has been used to estimate occupational exposure (NRC, 1983).

The metabolism of aniline has recently been studied _in vitro_ (Eyer et al., 1980; Blaauboer and van Holsteijn, 1983; Evelo et al., 1984). Perfusion of rat liver with radioactive aniline resulted in the identification of aniline, acetanilide, 4-acetamidophenol, 4-aminophenol, 2-aminophenol and acid-liberated aniline in the perfusate. Some radioactivity was observed bound to the liver. When red blood cells were added to the perfusion medium, phenylhydroxylamine and nitrosobenzene were also identified in the perfusate (Eyer et al., 1980). When aniline was added to the culture medium of shaker cultures of isolated hepatocytes, the amount of phenylhydroxylamine and nitrosobenzene increased linearly with time during the 2-hour observation period (Blaauboer and van Holsteijn, 1983). When aniline was added to the culture medium of shaker cultures of isolated hepatocytes in the presence of inorganic sulfate, the amount of 4-aminophenol and 4-aminophenol sulfate conjugate increased linearly with time during the 2-hour observation period (Evelo et al., 1984).

Barlow and Sullivan (1982) reviewed several studies indicating that the enzymes which ring-hydroxylated aniline were present in the human fetal liver, but not the placenta, by 6-7 weeks of gestation (Juchau and Pederson, 1973; Pelkonen et al., 1973; Juchau et al., 1973; Rane et al, 1973; Pelkonen, 1973; Rane and Ackermann, 1972). The enzymes that oxygenate the amine group of aniline to produce phenylhydroxylamine, and consequently methemoglobinemia, are also present in human fetal liver (Rane and Ackermann, 1972).

Turner et al. (1976) reported in an abstract that 2-aminophenol, 4-aminophenol, 2-acetaminophenol, 4-acetaminophenol and acetanilide were identified in sheep intestines after incubation with aniline.

4.4. EXCRETION

Aniline is excreted almost completely in the urine (Baranowska-Dutkiewicz, 1982). As reviewed in IARC (1974, 1982), various conjugates of 2- and 4-aminophenol were excreted in the urine after aniline exposure in all species tested, including the rabbit, rat, mouse, guinea pig, gerbil, hamster, cat and dog (Williams, 1959; Parke, 1960).

Within 48 hours of administering 10, 30 or 100 mg/kg bw ^{14}C-aniline hydrochloride to male rats, 96, 91 and 77%, respectively, of the administered radioactivity was recovered in the urine (Bus et al., 1978).

Although Boobis and Powis (1975) reported that the bile contained small quantities of aniline and free 4-aminophenol, both they and Irons et al. (1980) concluded that significant amounts of aniline were not excreted in the bile in rats. Kao et al. (1978) reported that significant excretion of aniline and its metabolites by rats, pigs and sheep occurred in the urine rather than the feces.

5. EFFECTS

5.1. CARCINOGENICITY

Groups of 50 male and 50 female Fischer 344 rats were treated with food contaminated with 0.3% (3000 ppm) or 0.6% (6000 ppm) of aniline hydrochloride for 103 weeks (NCI, 1978). Groups of 25 male and 25 female Fischer 344 rats were used as controls. The rats were ~6 weeks old at the start of treatment. Following a 4-5 week observation period, all rats were killed 107-110 weeks after the start of treatment. In the treated rats, the two sites that had an increased incidence of neoplasia were the spleen and the body cavity. As indicated in Table 5-1, several different mesenchymal tumors were associated with aniline treatment. As indicated in Table 5-2, rats often had tumors that occurred in multiple organs of the pleural and abdominal cavities. For male rats, NCI (1978) concluded that there was a statistically significant association between aniline hydrochloride treatment and the increased incidence of hemangiosarcomas in the spleen (Table 5-3), the increased incidence of splenic fibrosarcomas and sarcomas NOS (see Table 5-1), and the increased incidence of fibrosarcomas and sarcomas NOS in multiple organs of the body cavity (see Table 5-2.). In addition, there was a significant increase in the incidence of malignant pheochromocytomas in the male rats (controls, 2/24; low dose, 6/50; high dose, 12/44). For female rats, NCI (1978) concluded that there was a possible association between aniline hydrochloride treatment and the increased combined incidence of fibrosarcomas and sarcomas NOS of the spleen, and the increased combined incidence of fibrosarcomas and sarcomas NOS in multiple organs of the body cavity. The incidence of hemangiosarcoma or fibrosarcoma and sarcoma NOS in a pooled group of control male Fischer rats was 0/250. None of a pooled group of 249 female Fischer 344 rats had fibrosarcoma or sarcoma NOS in either the spleen or in multiple organs of the body cavity.

TABLE 5-1

The Incidence of Splenic Neoplasia in Aniline Hydrochloride-Treated Rats[a]

Neoplasia	Males			Females		
	Control (n=25)	Low Dose[b] (n=50)	High Dose[c] (n=48)	Control (n=24)	Low Dose[b] (n=50)	High Dose[c] (n=50)
Sarcoma NOS	0	4	2	0	0	3
Fibroma	0	7	6	0	0	0
Hemangiosarcoma	0	19	20	0	1	2
Lipoma	0	0	0	0	0	1
Hemangioma	0	0	0	0	0	1

[a] Source: NCI, 1978

[b] Low dose = 3000 ppm aniline hydrochloride

[c] High dose = 6000 ppm aniline hydrochloride

N = number of rats spleens examined

TABLE 5-2

The Incidence of Tumors in Multiple Organs Within the Abdominal and Pleural Cavities of Rats[a]

Neoplasia	Males			Females		
	Control (n=25)	Low Dose[b] (n=50)	High Dose[c] (n=48)	Control (n=24)	Low Dose[b] (n=50)	High Dose[c] (n=50)
Fibrosarcoma	0	2	8	0	1	3
Leiomyosarcoma	0	0	2	1	0	0
Hemangiosarcoma	0	0	1	0	0	0
Sarcoma NOS	0	0	1	0	0	1

[a] Source: NCI, 1978

[b] Low dose = 3000 ppm

[c] High dose = 6000 ppm

N = number of rats examined

TABLE 5-3

Carcinogenicity Evaluations of Rats and Mice Exposed to Aniline Hydrochloride[a]

Species/Strain	Sex	Dose (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mouse/B6C3F1	M	6,000	103	107	NR	NR	NA	NA	NA
		12,000	103	107	NA	NA	NA	NA	NA
	F	6,000	103	107	NR	NR	NA	NA	NA
		12,000	103	107	NR	NR	NA	NA	NA
Rat/ Fischer 344	M	3,000	103	107	NR	NR	spleen	hemangiosarcoma	19/50 (<0.001)
		6,000	103	108	NR	NR	spleen	hemangiosarcoma	20/46 (<0.001)
	F	3,000	103	107	NR	NR	spleen	hemangiosarcoma	1/50 (NS[b])
		6,000	103	108	NR	NR	spleen	hemangiosarcoma	2/50 (NS[b])

QUALITY OF EVIDENCE

Strengths of Study:	Appropriate route, adequate length of treatment and number of animals.
Weakness of Study:	None apparent
Overall Adequacy:	Adequate

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[a] Source: NCI, 1978

[b] Please see the text for possible biological significance.

NR = Not reported; NA = not applicable; NS = not statistically significant

In a recent reanalysis of the data generated by NCI (1978), Goodman et al. (1984) reported that aniline, along with five other aromatic amines or their derivatives, was associated with the induction of splenic and peritoneal sarcoma. Goodman et al. (1984) postulated that exposure of animals to aniline resulted in methemoglobin formation followed by splenic hemosiderosis which induced splenic fibrosis, a pre-conditioning factor in the development of splenic sarcoma (fibrosarcoma, osteosarcoma and hemangiosarcoma). Finally, the splenic sarcoma developed into metastatic foci of neoplasia within the body cavities (Goodman et al., 1984).

Also in the NCI (1978) study, groups of ~50 male and 50 female B6C3F1 mice were treated with food contaminated with 0, 0.6 (6000 ppm) or 1.2% (12,000 ppm) aniline hydrochloride for 103 weeks (see Table 5-3). There was no statistically significant increase in any type of tumor in male or female mice that was associated with aniline hydrochloride treatment.

Groups of 10-18 male Wistar rats were treated with 0.03-0.12% aniline in their drinking water for 80 weeks (Hagiwara et al., 1980). The age of the rats at the start of treatment was not reported. As indicated in Table 5-4, the incidence of forestomach papillomas was low and did not appear to be dose-related. One rat in the low-dose group (0.03% aniline in the drinking water) had a pituitary adenoma. No other tumors were reported.

As indicated in Table 5-5, a group of 50 rats was exposed to a dose of ~22 mg/day of aniline hydrochloride in drinking water (Druckrey, 1950). The treatment appeared to be continued for the lifetime of the rat. By day 425 of treatment, ~50% of the rats were dead; by day 750 of the experiment, all the rats were dead. No tumors were observed in the bladder, liver, spleen or kidneys, the only organs evaluated.

TABLE 5-4

Tumor Incidence of Male Wistar Rats Orally Exposed to Aniline[a]

Dose[b]	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
0	80	80	NR	H_2O	NA	NA	0/15
0.03	80	80	NR	H_2O	forestomach	papilloma	1/10
0.06	80	80	NR	H_2O	forestomach	papilloma	1/18
0.12	80	80	NR	H_2O	NA	NA	0/16

QUALITY OF EVIDENCE

Strengths of Study:	Attempts to corroborate the NCI (1978) study in male rats
Weakness of Study:	Length of treatment, size of treatment groups
Overall Adequacy:	Inadequate

---

[a] Source: Hagiwara et al., 1980

[b] Dose is given as % in the drinking water

NR = Not reported; NA = not applicable

TABLE 5-5

Tumor Incidence of Rats Orally Exposed to Aniline Hydrochloride*

Species/ Strain	Sex	Dose (mg/day)	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
NR	NR	22	425-750 days	425-750 days	NR	in H_2O	NA	NA	NA

QUALITY OF EVIDENCE

Strengths of Study: Appropriate route

Weakness of Study: No controls reported, only one dose tested

Overall Adequacy: Inadequate

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*Source: Druckrey, 1950

NR = Not reported; NA = not applicable

Groups of 15 male and 15 female Syrian golden hamsters received 52 weekly subcutaneous injections of 0 or 1.9 mmol/kg of aniline in peanut oil. Although the mean survival time was reduced in the aniline treated hamsters (males, 67.7 weeks; female, 68.7 weeks), no increased incidence of tumors was observed (Hecht et al., 1983).

5.2. MUTAGENICITY

As summarized in Table 5-6, aniline was negative in most of the reverse mutation assays using _Salmonella typhimurium_ (Miyata et al., 1981; Simmon, 1979a; DeFlora, 1981; Parodi et al., 1981; McCann et al., 1975; Hecht et al., 1979; Haworth et al., 1983; Garner and Nutman, 1977). In an abstract, Chung et al. (1981) reported that aniline was not mutagenic; however, the NRC (1983) review indicated that Mitchell (1978) reported aniline to be weakly positive in tests using _S. typhimurium_ TA98 and TA100 after metabolic activation and that Nagao et al. (1977) reported aniline to be positive in tests using _S. typhimurium_ only in the presence of norharman and metabolic activation. Sugimura et al. (1982) confirmed the mutagenicity of aniline in assays using _S. typhimurium_ only in the presence of norharman.

DNA-repair deficient strains and DNA-repair proficient strains of _Escherichia coli_ and _Bacillus subtilis_ did not display any substantially different response to aniline exposure (DeFlora et al., 1984; Mamber et al., 1983, 1984; McCarrol et al., 1981a,b). Simmon (1979b) reported that aniline did not induce mitotic recombination in the presence or absence of metabolic activation in _Saccharomyces cerevisiae_. The frequency of SCE was increased when male mice were treated with an intraperitoneal injection of 210 or 420 mg/kg of aniline (~0.5 and 1.0 times the LD_{50}, respectively, as indicated in Section 5.6.) and the bone marrow cells from the femur were

TABLE 5-6

Mutagenicity of Aniline

Assay	Indicator/ Organism/Strain	Application Method	Concentration or Dose	Activation System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium/ TA92,TA94,TA98,TA100, TA1535,TA1537	plate incorporation	0.03-3 mg/ plate	+/-	-/-	NC	Miyata et al., 1981
Reverse mutation	S. typhimurium/ TA98, TA100, TA1535, TA1536, TA1537, TA1538	plate incorporation	≤1000 μg/ plate	+/-	-/-	NC	Simmon, 1979a
Reverse mutation	S. typhimurium/ TA98, TA100, TA1535, TA1537, TA1538	plate incorporation	≤215,000 nmoles/plate	+/-	-/-	Aniline apppeared to be bacterio-toxic at the highest dose tested.	DeFlora, 1981
Reverse mutation	S. typhimurium/TA98, TA100	plate incorporation	100, 500 and 2500 μg/plate	+	-/-	NC	Parodi et al., 1981
Reverse mutation	S. typhimurium/TA98, TA100	NR	NR	+/-	(+)/-	Aniline was weakly positive in the liquid-medium assay with metabolic activation.	Mitchell, 1978
Reverse mutation	S. typhimurium/TA98, TA100, TA1535, TA1537	NR	NR	+/-	-/-	NC	McCann et al., 1975
Reverse mutation	S. typhimurium/TA98, TA100	NR	NR	+/-	-/-	NC	Hecht et al., 1979
Reverse mutation	S. typhimurium/TA1538	NR	NR	+/-	-/-	NC	Garner and Nutman, 1977
Reverse mutation	S. typhimurium/TA98, TA100, TA1535, TA1537	modified plate incorporation	≤10 mg/plate	+/-	-/-	NC	Haworth et al., 1977
DNA interaction	E. coli/WP2, WP67, CM871	spot test	NR	-	-	Aniline was equally toxic in the DNA repair-deficient and the DNA repair-proficient strains.	DeFlora et al., 1984
DNA interaction	E. coli/WP2, WP100	liquid medium	≤2000 μg/mL	+	-	0.1 mL of aniline was placed in a 12 mm wide well cut in the center of the agar plate containing the bacteria	Mamber et al., 1983, 1984
DNA interaction	E. coli/WP2, WP2uvrA, CM611, WP67, WP100, WP3100, P3478	liquid medium	≤800-2000 μg/ well[a]	+/-	-/-	Aniline was serially diluted and tested in consecutive rows of a microliter plate.	McCarrol et al., 1981a

TABLE 5-6 (cont.)

Assay	Indicator/ Organism/Strain	Application Method	Concentration or Dose	Activation System	Response	Comments	Reference
DNA interaction	*B. subtilis*/H17, M45	liquid medium	<200-400 µg/ well[a]	-	see comment	Although there was a difference between the DNA repair-deficient and DNA repair-proficient strains, aniline was considered negative because there was an insufficient volume in the micro-well to prepare a homogeneous suspension.	McCarroll et al., 1981b
Mitotic recombination	*S. cerevisiae*/D3	plate incorporation	1% v/v	+/-	-/-	NC	Simmon, 1979b
SCE	mice (bone marrow cells)/Swiss male	i.p. injection	0-420 mg/kg	NR	+	There was a dose-related increase in the number of SCEs seen after treatment with aniline.	Parodi et al., 1982, 1983
SCE	human fibroblasts/ GM-3468	in tissue culture medium	0-10 mM[b]	-	-	Although aniline hydrochloride did not increase the frequency of SCE, both 2-aminophenol and N-phenylhdroxylamine, two metabolites of aniline, did.	Wilmer et al., 1981
Forward mutation	mouse lymphoma cells/ TK+/-	in media culture	0-11.8x10^{-3} M	+	+	Although relatively small, there was a statistically significant increase in the frequency of forward mutations in mouse lymphoma cells in the presence of aniline.	Amacher et al., 1980

[a] The well that contained the test chemical in the microsuspension assay using microliter plates appeared to contain ~100 mg/ℓ of fluid.

[b] The sister chromatid exchange study by Wilmer et al (1981) used aniline hydrochloride rather than aniline.

NR = Not reported

analyzed 24 hours after treatment (Parodi et al., 1982, 1983). In an *in vitro* assay, however, aniline did not increase the frequency of SCE in human fibroblasts, although two metabolites of aniline, 2-aminophenol and N-phenylhydroxylamine, did significantly increase the frequency of SCE (Wilmer et al., 1981). Amacher et al. (1980) reported that aniline increased the frequency of forward mutations in mouse lymphoma cells in the presence of metabolic activation.

Several studies reported an increased frequency of SCE after aniline hydrochloride treatment of Chinese hamster pseudodiploid (Don) (Abe and Sasaki, 1977) and lung fibroblasts (Kawachi et al., 1980) *in vitro*. Chromosomal aberrations, however, did not appear to be induced by aniline hydrochloride in Chinese hamster pseudodiploid (Don) (Abe and Sasaki, 1977) or lung fibroblasts (Kawachi et al., 1980) *in vitro*. Aniline transformed Balb/3T3, a mouse cell line, but not Syrian hamster embryo cells or Fischer 344 rat embryo cells infected with a murine leukemia virus in the 15th-40th passages (Dunkel et al., 1981). IARC (1982) indicated in its review that Syrian hamster embryo cells (Pienta, 1980) or baby hamster kidney cells (BHK 21) were not transformed *in vitro* when cultivated in the presence of aniline. Pienta and Kawalek (1981) reported that Syrian golden hamster embryo cells were not transformed after cultivation with 0.01-10 µg of aniline/mℓ of tissue culture medium.

Boido et al. (1980) reported in an abstract that aniline was mutagenic in *S. typhimurium* after preincubation with human gastric juice, $NaNO_3$ and 4-aminoantipyrine.

5.3. TERATOGENICITY

A group of 50 pregnant CD-1 mice was treated daily from days 7-14 of gestation by gavage with 560 mg/kg/day of aniline (Borriston Labs, 1983). The control group of 50 pregnant CD-1 mice was treated by gavage with corn oil daily on days 7-14 of pregnancy; this group also served as a control group for two additional groups of 50 pregnant mice, one of which was treated with 4-nitroaniline, the other with N,N-dimethylaniline. The day on which the vaginal plug was first observed was designated day 1 of gestation. The aniline-treated and the control mice were allowed to deliver their litters. All mice were terminated 4 days after the birth of the pups. Maternal body weight, signs of maternal toxicity and mortality, and pup counts and weights on the day of birth and 3 days later at the termination of the experiment were recorded. As indicated in Table 5-7, six of the pregnant mice treated with 560 mg/kg/day of aniline died during pregnancy. Some of the mice that died were reported to have shown signs of prostration, tumors, ataxia, lethargy, piloerection, vaginal secretion or anal bleeding before death. As indicated in Table 5-8, although there was a significant difference in the total body weight gain between aniline-treated and control mice, there was no significant difference between the body weight of aniline-treated mice and the body weight of control mice throughout pregnancy. If there had been fertilization without implantation as indicated in Table 5-7, it is doubtful that the corpora lutea would be apparent 3 weeks later, since the lifespan of an unstimulated corpus luteum in the mouse has been reported to be ~4 days (Peters and McNatty, 1980). Therefore, the presence of corpora lutea in the ovaries ~23 days after mating does not indicate that "fertilization had occurred without subsequent implantation," as stated in the Borriston Labs (1983) report. If the total number of offspring produced in the aniline-treated group (250) is compared with the

TABLE 5-7

Comparison Between the Aniline-Treated and Control Mice During Pregnancy[a]

No. of Mice Studies	Vehicle Control Corn Oil (5 mℓ/day)	Aniline (560 mg/kg/day)
No. treated	50	50
No. of deaths	0	6
No. not pregnant	9	11
No. pregnant	41	25
Fertilization without subsequent implantation[b]	0	8
Live litters	41	25
Dead litters	0	0
Resorbed litters	0	0
Delivery index[c]	41/41	25/25
Percent	100	100

[a] Source: Borriston Labs, 1983

[b] Determined by the presence of corpora lutea upon examination of uteri at necropsy.

[c] Number of live litters produced per total number pregnant, excluding mice that were fertilized without subsequent implantations.

TABLE 5-8

Summary of Mean Maternal Weights, Litter Weights, Pup Counts and Offspring Viability Data[a]

Parameter Measured	Control (n=41)		Aniline (560 mg/kg/day) (n=25)	
	Mean	SD	Mean	SD
Maternal body weights (g)				
Gestation day 2	26.8	1.6	26.9	1.4
Gestation day 7	29.0	1.6	29.2	1.7
Gestation day 18	47.7	6.3	45.0	3.8
Weight change (day 18-7)	18.7	5.3	15.8[b]	3.8
Terminal (day 4 postpartum)	37.5	3.5	36.3	3.1
Litter weights (g)				
Birth	14.7	4.5	15.1	3.3
Day 3 postpartum	23.9	6.5	22.4	4.4
Weight change day 3-birth	9.2	2.7	7.3	4.4
Mean pup weight				
Birth	1.6	0.2	1.5	0.1
Day 3 postpartum	2.7	0.5	2.3	0.3
Weight change	1.1	0.4	0.8	0.2
Number of pups per litter at birth				
Live	9	3	10	2
Dead	0	1[c]	0	0
Total	9	3	10	3
Number of pups per litter on day 3 postpartum				
Live	9	3	10	3
Dead	0	0	1[b]	2
Offspring viability ratio (No. live pups on day 3: no. live pups at birth)	1.00	0.02	0.94[b]	0.16

[a] Source: Borriston Labs, 1983

[b] Significantly different from the control group at the level of $p<0.05$ (student's t-test)

[c] As appeared in the report; most likely typographical error

SD = Standard deviation; N = number

total number of offspring produced in the control group (369), assuming there is a mean of 10 and 9 pups per litter in the aniline-treated and control groups, respectively (see Table 5-8), treatment of pregnant mice by gavage with aniline on days 7-14 of pregnancy appeared to have caused a decrease in the total number of pups born even though the average number of pups per litter was not affected. Despite no description of the pregnancy status of the six aniline-treated mice that died, the data indicated that there were fewer pups produced in the aniline-treated group than in the control group. In addition, canni- balism was more prevalent in the aniline-treated group (5/25 litters) than in the control group (2/41 litters). Birth weight and postpartum weight gain were decreased in the aniline treated group and survival of the pups was significantly decreased in the aniline-treated group during the first 3 days postpartum. In conclusion, it appears that treatment of pregnant mice by gavage with 560 mg/kg of aniline on days 7-14 of pregnancy had an adverse effect on reproduction, regardless of the conclusion reported by Borriston Labs (1983).

In a review of the reproductive effects of aniline in the work place, Barlow and Sullivan (1982) reported that a Russian epidemiological study (Podluzhnyi, 1979) of 1264 female aniline dye industry workers indicated that, although there may be a correlation between exposure to organics and the incidence of menstrual disturbances and ovarian dysfunction, the nutritional status of the industrial worker played a significant role in determining whether or not adverse effects would develop after occupational exposure to aniline and other chemicals. The same Russian study (Podluzhnyi, 1979) reported an increased abortion rate for women working in the aniline dye industry, but interpretation of the results is confounded by the amount of strenuous physical exertion required in a particular job (Barlow and Sullivan, 1982).

Barlow and Sullivan (1982) referred to the work of Maickel and Snodgrass (1973) to indicate that aniline crosses the placenta in the rat and reaches equilibrium between maternal and fetal plasma within 1 hour of subcutaneous injection.

Aniline caused malformations when injected into the inner shell membrane of 3-day-old chick embryos (Korhonen et al., 1983).

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of aniline were not located in the available literature as cited in the Appendix.

5.5. CHRONIC TOXICITY

Groups of 50 male and 50 female Fischer 344 rats were treated with food contaminated with 0.3% (3000 ppm) or 0.6% (6000 ppm) aniline hydrochloride for 103 weeks (NCI, 1978). Following a 4-5 week observation period, all rats were killed 107-110 weeks after the start of treatment. Groups of 25 male and 25 female 344 Fischer rats were used as control. The rats were ~6 weeks old at the start of the treatment. There appeared to be a dose-related decrease in body weight in the females, which may be significant at the high-dose level; the decreased body weight seen in the high-dose males did not appear to be significant. The aniline-contaminated diets did not affect the survival rate of the rats. As indicated in Table 5-9, there was an increased incidence of splenic hyperplasia and erythropoiesis that may be associated with the increased incidence of splenic tumorigenesis discussed in Section 5.1. Renal and hepatic hemosiderosis was also reported. These four non-neoplastic lesion were seen both male and female rats with a slightly higher incidence in the female rats.

TABLE 5-9

Incidence of Non-neoplastic Lesions in Fischer 344 Rats Exposed to Dietary Aniline Hydrochloride*

Lesion	Males			Females		
	Control	Low Dose (3000 ppm)	High Dose (6000 ppm)	Control	Low Dose (3000 ppm)	High Dose (6000 ppm)
Splenic hyperplasia	0/25	18/50	7/46	0/23	23/50	28/50
Splenic erythropoiesis	0/25	6/50	5/46	0/23	36/50	30/50
Hepatic hemosiderosis (Kupffer cells)	0/25	2/50	26/47	0/24	0/50	29/50
Renal hemosiderosis	0/25	21/50	34/48	0/23	46/50	45/50

*Source: NCI, 1978

Groups of ~50 male and 50 female B6C3F1 mice were treated with food contaminated with 0, 0.6 or 1.2% aniline hydrochloride for 103 weeks. The treated mice were killed 4 weeks later, 107 weeks after the start of the experiment; the controls were killed 109 weeks after the start of the experiment. The mice were ~6 weeks old at the start of treatment. The aniline-contaminated diets did not significantly affect the life span of the mice, but body weights were depressed in male mice. As summarized in Table 5-10, the only non-neoplastic lesion observed in male mice was an increased incidence of chronic diffuse inflammation of the bile duct. In female mice, there was an increased incidence of splenic erythropoiesis and hydrometra, an accumulation of serous fluid in the uterine cavity, in the high-dose group only (NCI, 1978).

In a study designed to test the interaction between aniline and norharman, groups of 10-18 male Wistar rats were treated with 0.03-0.12% aniline in their drinking water for 80 weeks (Hagiwara et al., 1980). The age of the rats at the start of the treatment was not reported. As indicated in Table 5-11, aniline did not affect the body weight nor the relative or absolute liver weight in rats drinking aniline-contaminated water. Data reported by Hagiwara et al. (1980), but not included in Table 5-11, indicated that aniline did not affect the relative or absolute kidney weight, the white blood cell count, the serum glutamic oxaloacetic transaminase, the serum glutamic pyruvic transaminase, the serum alkaline phosphatase, the total serum protein or the blood urea nitrogen levels. Hagiwara et al. (1980) reported that hematological values were not affected by aniline treatment, but their data (see Table 5-11) indicate that there is a doserelated decrease in the red blood cell count, hemoglobin level and hematocrit of rats drinking aniline-contaminated water.

TABLE 5-10

Incidence of Non-neoplastic Lesions in B6C3F1 Mice Exposed to Dietary Aniline Hydrochloride[a]

Lesion	Males			Females		
	Control	Low Dose[b]	High Dose[c]	Control	Low Dose[b]	High Dose[c]
Chronic diffuse inflammation of the bile duct	0/39	14/49	13/49	None	None	None
Splenic erythropoiesis	None	None	None	4/45	6/48	13/49
Hydrometra (uterus)	NA	NA	NA	0/44	1/46	5/43

[a] Source: NCI, 1978

[b] Low dose = 6000 ppm

[c] High dose = 12,000 ppm

NA = Not available

TABLE 5-11

The Effects of Aniline Contaminated Water[a]

Treatment	No. of Rats at Start	Effective No. of Rats	Body Weight (g)	Liver Weight		Red Blood Cell ($X10^{-4}$)	Hemoglobin (mg/dℓ)	Hematocrit (%)
				Absolute (g)	Relative (g)			
Control	28	15	517 ± 64	14.4 ± 2.6	2.7 ± 0.2	827 ± 57	18.4 ± 1.4	43.5 ± 2.0
0.03[b]	28	10	580 ± 140	17.7 ± 5.5	3.0 ± 0.4	708 ± 53	18.2 ± 0.7	47.0 ± 3.9
0.06[b]	28	18	568 ± 75	16.8 ± 2.8	2.9 ± 0.3	667 ± 56	17.7 ± 1.1	44.5 ± 2.7
0.12[b]	28	16	564 ± 107	16.0 ± 2.9	2.8 ± 0.2	651 ± 17	15.4 ± 1.9	36.8 ± 4.7

[a] Source: Hagiwara et al., 1980

[b] % Aniline added to the drinking water

5.6. OTHER RELEVANT INFORMATION

The LD_{50} values of aniline administration by oral, inhalation and dermal routes of exposure are listed in Table 5-12.

A short-term study in which a single oral dose of 0, 20, 40, 100, 200, 300 or 1000 mg/kg of aniline was given to Colworth-Wistar male rats 12 days before killing the animals indicated that aniline increased splenic weight, splenic erythropoietic activity, splenic sinusoidal engorgement and splenic hemosiderin content at doses >20 mg/kg (Jenkins et al., 1972). The rats were 5 weeks old at the start of treatment. Although there was a slight increase in hepatic hemosiderin content and erythropoietic activity, no gross pathological changes were noted in the liver or kidney (Jenkins et al., 1972).

When groups of 6-8 male Fischer 344 rats were treated with a daily oral dose of 110 mg/kg of aniline for 5, 10 or 20 days, splenic (but not body) weight was significantly increased (Short et al., 1983). Histological evaluation revealed a significant increase in splenic congestion and hematopoiesis and in bone marrow cellularity at all time points studied. Splenic hemosiderosis increased significantly only after the rats had ingested aniline for 20 days. The liver did not appear to be adversely affected in this study. The rats were almost 11 weeks old at the start of treatment (Short et al., 1983).

Increased methemoglobin formation occurred in volunteers after single oral ingestion of 25-65 mg of aniline, but not after ingestion of 5 or 15 mg of aniline (Jenkins et al., 1972). Heinz bodies were not detected after aniline treatment at any of the single dose levels reported (5, 15, 25, 35, 45, 55 and 65 mg/human). Jenkins et al. (1972) concluded that aniline was more toxic in humans than in rats. According to their experiments, the oral

TABLE 5-12

Acute Toxicity of Aniline

Route	Species	LD$_{50}$	Reference
Oral	rat (male)	440 mg/kg	Jacobson, 1972
Oral	rat	1072 mg/kg	Sax and Feiner, 1984
Oral	mouse	841 mg/kg	Sax and Feiner, 1984
Inhalation	rat	LC$_{50}$ 950 mg/m^3 (250 ppm) for 4 hours	Carpenter et al., 1949
Dermal	guinea pig	1320 mg/kg	Roudabush et al., 1965

no-effect level in the rat was 20 mg of aniline/kg bw, corresponding to a human dose of ~1400 mg of aniline, but the oral no-effect level experimentally determined in volunteers was 15 mg of aniline/human.

Occupational exposure to aniline, usually by inhalation or percutaneous routes of exposure, results in methemoglobin formation and consequent cyanosis and respiratory distress (ACGIH, 1980). A woman who had sat in a car seat saturated with an aniline-containing, high-octane booster developed cyanosis, dyspnea, fatigue and dizziness. The initial methemoglobin level was reported to be 53%; recovery occurred within 24 hours after methylene blue treatment (Whelan, 1984). Ingestion of aniline-contaminated cooking oil in Spain led to an epidemic characterized by fever, pruritis, adenopathy, hepatomegaly, rash, conjunctivitis and respiratory distress (Casado deFrias et al., 1983; Tabuenca, 1981; Ross, 1981). Although aniline was reported as the main contaminant, other toxic chemicals such as methylamine, quinoline, azobenzene, methylquinoline and dimethylquinoline, were also identified in the contaminated oil (Ross, 1981).

Microsomal metabolism of aniline was enhanced by acetone (Powis et al., 1977) and cyanide (Kamataki et al., 1980), but was inhibited by manganese (Schnell and Deimling, 1984). Aniline increased the clastogenicity of benzene and slightly altered its metabolism (Harper et al., 1984). The Russians have investigated the effects of aniline treatment in combination with various other chemicals. A more pronounced alteration of enzyme patterns was noted in rats treated orally with aniline and nitrosodimethylamine for 4 weeks than with either compound alone (Markur'eva et al., 1982). Abstracts of Russian work indicated that cysteamine prevented methemoglobinemia in dogs treated with aniline (Loboda and Voitenko, 1972), that sodium alkyl sulfate increased the toxicity of aniline that had been administered in the drinking water (Litvinov, 1974) and that aniline enhanced the tumorigenicity of nitrosodimethylamine (Litvinov et al., 1984).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethal effects of aniline were determined in rainbow trout, Salmo gairdneri, during 96-hour tests in hard (320 mg $CaCO_3$/ℓ) and soft (20 mg $CaCO_3$/ℓ) water (Calamari et al., 1980). The 96-hour LC_{50} values were 41 and 20 mg aniline/ℓ, respectively, for the different water conditions. Hodson et al. (1984) reported 96-hour LC_{50} (waterborne aniline), intraperitonal LD_{50} and oral intubation LD_{50} values for aniline in rainbow trout. The 96-hour LC_{50} was 36.2 mg/ℓ water, while the intraperitoneal LD_{50} and oral LD_{50} values were 1.35 and 1.30 g/kg bw, respectively. Abram and Sims (1982) determined the toxicity of aniline in rainbow trout during tests of 12 hours to 7 days duration. The water hardness was 250 mg $CaCO_3$/ℓ. The respective LC_{50} values for 12 hours, 1, 2, 4 and 7 days of exposure were 46.0, 30.5, 28.3, 10.6 and 8.2 mg aniline/ℓ. Slooff et al. (1983) conducted toxicity tests using several species of freshwater fish exposed to aniline for 48 hours. NOLC values and LC_{50} values were reported. The NOLC values in rainbow trout (S. gairdneri), guppies (Poecilia reticulata), medaka (Oryzias latipes) and fathead minnows (Phimephals promelas) were 36, 52, 100 and 45 mg aniline/ℓ, respectively. The respective 48-hour LC_{50} values were 43, 100, 165 and 65 mg aniline/ℓ for the four species. The 48-hour LC_{50} for the golden orfe, Leuciscus idus, was 49 mg aniline/ℓ, but an NOLC was not determined (Slooff et al., 1983). In the medaka, O. latipes, static 24- and 48-hour LC_{50} values were 74 and 48 mg aniline/ℓ, respectively (Tonogai et al., 1982). Wellens (1982) reported a 48-hour LC_{50} for the golden orfe, L. idus, of 61-78 mg aniline/ℓ and a 96-hour LC_{50} of 32-53 mg/ℓ for the zebrafish, Brachydanio rerio. The 48-hour LC_0, LC_{50} and

LC_{100} values for the golden orfe, L. idus, reported by Juhnke and Luedemann (1978) were 20-52, 61-65, and 92 mg aniline/ℓ, respectively.

Two species of amphibians, the clawed toad, Xenopus laevis, and the Mexican axolotl, Ambystoma mexicanum, were exposed to aniline for 2 days at various concentrations (Slooff and Baersolman, 1980). The 48-hour LC_{50} values for 3- to 4-week-old larvae were 560 and 440 mg/ℓ, respectively, for the clawed toad and axolotl. The NOLC values for these two species were 390 and 360 mg aniline/ℓ, respectively (Slooff et al., 1983).

In the water flea, Daphina magna, toxicity tests have been conducted by Bringmann and Kuehn (1977a, 1982) Calamari et al. (1980) and Slooff et al. (1983). The 24-hour LC_0, LC_{50} and LC_{100} values determined in D. magna were 0.13, 0.5 and 250 mg aniline/ℓ (Bringmann and Kuehn, 1977a). Bringmann and Kuehn (1982) reported 24-hour EC_0, EC_{50} and EC_{100} values of 0.06, 0.6-70 and 250-500 mg aniline/ℓ. Calamari et al. (1980) reported a 24-hour EC_{50} for immobilization of 23.0 mg aniline/ℓ. Slooff et al. (1983) reported NOLC values of 0.34 and 0.07 mg aniline/ℓ for D. magna and Daphnia pulex. The 48-hour LC_{50} values for D. magna, D. pulex and Daphnia cucullata were 0.64, 0.10 and 0.68 mg aniline/ℓ, respectively.

Slooff et al. (1983) reported that the 48-hour LC_{50} values in two insect larvae, Aedes aegypti and Culex pipiens, were 155 and 94 mg/ℓ, while NOLC values were 75 and 58 mg aniline/ℓ, respectively. Franco et al. (1984) reported 48-hour LC_{50} values at 400, 428, 478 and 272 mg aniline/ℓ, respectively, for four species of chironomid midge larvae, Chironomus tentans, Einfeldia natchitocheae, Clinotanypus pinguis and Tanypus neopunctipennis. In the freshwater mollusk, Lymnaea stagnalis, and thehydra, Hydra oligactis, 48-hour LC_{50} values were 800 and 406 mg aniline/ℓ and NOLC values were 560 and 235 mg/ℓ, respectively (Slooff et al., 1983).

Lethality tests conducted for 96 hours using the marine shrimp, *Crangon septemspinosa*, and the marine clam, *Mya orenaria*, were conducted by McLeese et al. (1979). Shrimp were exposed at levels as high as 55 mg aniline/ℓ, with a lethality threshold of 29.4 mg aniline/ℓ reported following 96-hour tests. In the clam, maximum exposure was also 55 mg/ℓ but no mortality occurred. The "closing" behavior of clams may have accounted for their survival by decreasing exposure.

6.2. CHRONIC EFFECTS

Embryo-larval toxicity tests of aniline were conducted by Birge et al. (1979) on largemouth bass (*Micropterus salmoides*), goldfish (*Carassius auratus*) and channel catfish (*Ictalurus punctatus*). Tests were conducted in soft (50 mg Ca CO_3/ℓ) and hard (200 mg $CaCO_3$/ℓ) water for 4 days. Hatching success and survival at 4 days posthatching were reported. The LC_{50} values for survival of larvae at 4 days posthatching (4 days of exposure) were 11.8, 5.5 and 5.0 mg aniline/ℓ in soft water and 7.1, 4.6 and 6.2 mg aniline/ℓ in hard water, respectively, in bass, goldfish and catfish. The LC_{50} values for suvival at hatching were 32.7, 9.3 and 5.5 mg aniline/ℓ in soft water and 29.9, 7.6 and 6.3 mg/ℓ in hard water, respectively, for the three species. Substantial teratogenic effects in larvae were evident when aniline concentrations of 34-100 mg/ℓ were used (Birge et al., 1979).

The lethal and teratogenic effects of aniline on embryos of the clawed toad, *X. lasvis*, were determined by Dumont et al. (1979) and Davis et al. (1981). Exposure to 10 mg aniline/ℓ for 4 days resulted in 11% abnormal embryos and 28% mortality, while no abnormalities or deaths occurred among controls. Exposure at 50 mg aniline/ℓ resulted in fewer abnormal embryos (6%) and fewer deaths (4% mortality). Davis et al. (1981) reported LC_{50}

values for aniline in various stages of X. laevis embryos. Early embryos, exposed from the mid-blastula stage, had 24-, 48-, 72-, 96- and 120-hour LC_{50} values of 1400, 660, 490, 550 and 500 mg aniline/ℓ, respectively. Tailbud embryos had 24-, 48-, 72- and 96-hour LC_{50} values of 1620, 1350, 1150 and 940 mg aniline/ℓ. Swimming larvae appeared most sensitive, having 48-, 72-, 90- and 120-hour LC_{50} values of 1400, 540, 150 and 95 mg aniline/ℓ, respectively.

Aniline at a concentration of 0.2 mg/ℓ caused death in Daphnia magna within 9 days of exposure (Lakhnova, 1975) and toxicity involved the nervous and digestive systems and reproduction. Hattori et al. (1984) conducted 14-day tests of aniline using reproduction in Daphnia as a measure of toxicity. Aniline at 0.66 mg/ℓ had a significant effect on the rate of reproduction in the daphnids.

The toxicity threshold level for the chironomid midge larvae, Chironomus dorsalis, was 3 mg aniline/ℓ; 6 mg aniline/ℓ caused mortality (Puzikova and Markin, 1975).

6.3. PLANT EFFECTS

Calamari et al. (1980) reported that the 96-hour EC_{50} for decreased growth in the alga, Selenastrum capricornutum, was 19 mg aniline/ℓ. Carbon fixation in S. capricornutum was decreased to 90, 34 and 3% of controls following exposure to 10, 100 and 1000 mg aniline/ℓ for 4 hours (Giddings, 1979). Broda and Dombrowicz (1982) reported that the toxicity threshold for inhibited growth in Chlorella pyrenoidosa was 1.96-3.76 mg aniline/ℓ. Slooff et al. (1983) reported NOEC values of 11, 8, 16 and 10 mg aniline/ℓ for C. pyrenoidosa, Scenedesmus pennonicus (192-hour exposure), S. pennonicus (48-hour exposure) and S. capricornutum, respectively. The toxicity threshold for inhibited cell multiplication in Scenedesmus quadricauda was 8.3 mg aniline/ℓ (Bringmann and Kuehn, 1977b, 1980). Using the algal lawn growth technique with Agmenellum quadruplicatum, Batterton et al. (1978) reported that as little as 10 μg aniline per disk (36 mm) caused complete growth inhibition. Partial inhibition was reported at 1 μg/plate.

6.4. RESIDUE

Calamari et al. (1980) reported 100% disappearance of aniline when solutions of 10, 50 and 100 mg/ℓ were inoculated with various bacterial treatments and incubated for 14 days.

Ogawa et al. (1983) reported that aniline levels in fish increased proportionally to their ambient concentration, but accumulation was not evident. In green algae, Chlorella fusca, a bioconcentration value of 4 was reported after a 24-hour exposure to 0.050 mg aniline/ℓ (Geyer et al., 1981).

6.5. OTHER RELEVANT INFORMATION

The toxicity threshold levels for cell multiplication in bacteria, Pseudomonas putida, and protozoa, Entosiphon sulcatum, were 130 and 24 mg aniline/ℓ, respectively (Bringmann and Kuehn, 1977b, 1980). Slooff et al. (1983) reported NOEC values of 130 and 0.16 mg aniline/ℓ in the bacteria, Pseudomonas putida, and cyanobacterium, Microcystis aeruginosa. In the protozoan species, E. sulcatum, Uronema porduczi and Chilomonas paramecium, NOEC values were 24, 90 and 250 mg aniline/ℓ, respectively.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1983) has recommended a TWA-TLV of 2 ppm (10 mg/m³) and a STEL of 5 ppm (20 mg/m³), with the skin notation indicating that significant amounts of aniline can be absorbed through the skin despite adequate respiratory protection. According to the ACGIH (1983), the current TLV was based on the work of a Polish scientist (Dutkiewicz, 1962). The NIOSH/OSHA (1978) guidelines reported a standard of 5 ppm (19 mg/m³) for exposure to aniline.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of aniline were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Aniline was not mutagenic in most of the bacterial mutagenicity assays regardless of the presence or absence of metabolic activation, however, aniline did cause increased frequencies of SCE *in vivo* (Parodi et al., 1982, 1983) and in two *in vitro* assays (Abe and Sasaki, 1977; Kawachi et al., 1980). In another *in vitro* assay, the metabolites of aniline, but not aniline itself, increased the frequency of SCE (Wilmer et al., 1981). Borriston Labs (1983) reported increased pup mortality in mice treated with aniline during pregnancy. The Borriston Labs (1983) study emphasized the need to evaluate the effect of aniline exposure during pregnancy on the number of live pups born and the ability of the newborn to survive after aniline exposure *in utero*. No completely satisfactory chronic or subchronic toxicity studies on aniline have been reported. Data reported in the NCI (1978) study indicated that chronic exposure to aniline decreased body weight gain, increased hemosiderosis in the liver and kidney and resulted in splenic hyperplasia and increased erythropoiesis in male and female rats. Splenic erythropoiesis was observed in female mice treated with the high dose of aniline, but not in the male mice. The only non-neoplastic treatment-related lesion in male mice was chronic diffuse inflammation of the bile duct (NCI, 1978). Although weight changes in either body weight gain or splenic weight were not reported in the 80-week rat study by Hagiwara et al. (1980), hemoglobin levels and the red blood cell count appeared depressed after chronic aniline exposure.

Although no longer considered a bladder carcinogen (IARC, 1974, 1982), ingestion of 3000 or 6000 ppm of dietary aniline hydrochloride during a 2-year study significantly increased the incidence of splenic hemangiosarcoma in male rats (NCI, 1978). The incidence of splenic tumors was also observed in female rats. No increased incidence of any tumor type was reported in male or female mice (NCI, 1978). Rats that drank aniline-contaminated water for 80 weeks did not have an increased incidence of any type of tumor (Druckrey, 1950; Hagiwara et al., 1980).

According to IARC (1982), there is "limited evidence" for the carcinogenicity of aniline in experimental animals. Epidemiological data on the carcinogenicity of aniline in humans are insufficient, and IARC (1982) has categorized aniline as a group 3 chemical meaning that while there may be limited carcinogenicity data, overall the data are inadequate to access the human carcinogenic potential. Based on U.S. EPA (1984) guidelines, aniline can be classified as group C, a possible human carcinogen.

Data used to calculate the q_1* values are summarized in Tables 8-1 to 8-5. To obtain the transformed doses of 103.58 and 207.17 mg/kg/day, the dietary exposure levels in ppm were multiplied by the ratio of the length of aniline hydrochloride exposure in days to the length of the experiment in days (721/753), by the ratio of the molecular weights of aniline and aniline hydrochloride (93.13/129.60) and by the amount of food consumed per day by a rat estimated to be equivalent to 5% of its body weight. The animal q_1* was calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The human q_1* was derived by multiplying the animal q_1* by the cube root of the ratio of the human to animal body weights (assumed to be 70/0.35) and the ratio of the length of the experiment to the lifespan of the animal which, in this case, is 1.

As indicated in Table 8-6, a q_1* for humans was derived for the incidence of hemangiosarcoma in the spleen, the incidence of hemangiosarcoma in the spleen and body cavities, and the combined incidence of fibrosarcoma and sarcoma NOS in the spleen, in the body cavities, and in the spleen and body cavities together. The highest q_1^*, 2.6×10^{-2} $(mg/kg/day)^{-1}$, based on hemangiosarcoma of the spleen in male rats is suggested as the most protective estimate of the carcinogenic potency of aniline.

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: Aniline Hydrochloride

Reference: NCI, 1978

Species, Strain, Sex: rat, Fischer 344, male (1)

Body weight: 0.35 kg, measured

Length of exposure (l_e): 721 days

Length of experiment (L_e): 749-756 days

Lifespan of animal (L): 749-756 days

Tumor site and type: spleen hemangiosarcoma

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)		Transformed Dose (mg/kg/day)	Incidence
Aniline Hydrochloride (mol.wt.=129.60)	Aniline (mol.wt.=93.13)		No. Responding/No. Tested or Examined
0	0	0	0/25
3000	(721/753) 2163.6335	103.58	19/25
6000	(721/753) 4327.2671	207.17	20/46

Unadjusted q_1^* from study = $4.4389\text{x}10^{-3}$ $(\text{mg/kg/day})^{-1}$
Human q_1^* = $2.5959\text{x}10^{-2}$ $(\text{mg/kg/day})^{-1}$

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: Aniline Hydrochloride

Reference: NCI, 1978

Species, Strain, Sex: rat, Fischer 344, male (2)

Body weight: 0.35 kg, measured

Length of exposure (l_e): 721 days

Length of experiment (L_e): 749-756 days

Lifespan of animal (L): 749-756 days

Tumor site and type: spleen, fibrosarcoma or sarcoma NOS (combined incidence)

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)			Incidence
Aniline Hydrochloride (mol.wt.=129.60)	Aniline (mol.wt.=93.13)	Transformed Dose (mg/kg/day)	No. Responding/No. Tested or Examined
0	0	0	0/25
3000	(721/753) 2163.6335	103.58	7/50
6000	(721/753) 4327.2671	207.17	9/46

Unadjusted q_1^* from study = 1.7601×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 1.02933×10^{-2} $(mg/kg/day)^{-1}$

TABLE B-3

Cancer Data Sheet for Derivation of q_1*

Compound: Aniline Hydrochloride

Reference: NCI, 1978

Species, Strain, Sex: rat, Fischer 344, male (3)

Body weight: 0.35 kg, measured

Length of exposure (l_e): 721 days

Length of experiment (L_e: 749-756 days

Lifespan of animal (L): 749-756 days

Tumor site and type: body cavities, fibrosarcoma and sarcoma NOS

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)		Transformed Dose (mg/kg/day)	Incidence
Aniline Hydrochloride (mol.wt.=129.60)	Aniline (mol.wt.=93.13)		No. Responding/No. Tested or Examined
0	0	0	0/25
3000	(751/753) 2163.6335	103.58	2/50
6000	(721/753) 4327.2671	207.17	9/48

Unadjusted q_1* from study = 1.0568×10^{-3} $(mg/kg/day)^{-1}$
Human q_1* = 6.18×10^{-3} $(mg/kg/day)^{-1}$

TABLE 8-4

Cancer Data Sheet for Derivation of q_1^*

Compound: Aniline Hydrochloride

Reference: NCI, 1978

Species, Strain, Sex: rat, Fischer 344, male (4)

Body weight: 0.35 kg, measured

Length of exposure (l_e): 721 days

Length of experiment (L_e): 749-756 days

Lifespan of animal (L): 749-756 days

Tumor site and type: spleen and body cavities, hemangiosarcoma

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)		Transformed Dose (mg/kg/day)	Incidence
Aniline Hydrochloride (mol.wt.=129.60)	Aniline (mol.wt.=93.13)		No. Responding/No. Tested or Examined
0	0	0	0/25
3000	(721/753) 2163.6335	103.58	19/50
6000	(721/753) 4327.2671	207.17	21/48

Unadjusted q_1^* from study = 4.4224×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 2.58625×10^{-2} $(mg/kg/day)^{-1}$

TABLE 8-5

Cancer Data Sheet for Derivation of q_1^*

Compound: Aniline Hydrochloride

Reference: NCI, 1978

Species, Strain, Sex: rat, Fischer 344, male (5)

Body weight: 0.35 kg, measured

Length of exposure (l_e): 721 days

Length of experiment (L_e): 749-756 days

Lifespan of animal (L): 749-756 days

Tumor site and type: spleen and body cavities, fibrosarcoma and sarcoma NOS

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)		Transformed Dose (mg/kg/day)	Incidence
Aniline Hydrochloride (mol.wt.=129.60)	Aniline (mol.wt.=93.13)		No. Responding/No. Tested or Examined
0	0	0	0/25
3000	(721/753) 2163.6335	103.58	5/50
6000	(721/753) 4327.2671	207.17	18/48

Unadjusted q_1^* from study = 1.8253×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 1.06743×10^{-2} $(mg/kg/day)^{-1}$

TABLE 8-6

Carcinogenicity of Aniline in Male Fischer 344 Rats

Tumor Type	Human q_1^* $(mg/kg/day)^{-1}$
Hemangiosarcoma in the spleen	2.60×10^{-2}
Fibrosarcoma and sarcoma NOS in the spleen	1.03×10^{-2}
Fibrosarcoma and sarcoma NOS in the body cavities	6.18×10^{-3}
Hemangiosarcoma in the spleen and body cavities	2.59×10^{-2}
Fibrosarcoma and sarcoma NOS in the spleen and body cavities	1.07×10^{-2}

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

As discussed in Section 5.5., there are no adequate studies on the chronic toxicity of aniline.

The NCI (1978) study is primarily a carcinogenicity study; the Hagiwara et al. (1980) study was designed to evaluate the interaction of aniline and norharman exposure. The effects of aniline treatment in mice and rats are summarized in Table 9-1. The NCI (1978) study reported decreased body weight gain in male and female rats and in male mice, which did not appear to be tumor-related. The increased renal and hepatic hemosiderosis reported in rats did not appear tumor-related since no tumors were reported in these organs (NCI, 1978). The teratogenicity study (Borriston Labs, 1983) discussed in Section 5.3. indicated that the survival of newborns whose mothers had been treated by gavage with aniline was decreased. The CSs for aniline are reported in Table 9-1. The highest CS, associated with an RQ of 1000, was obtained from the teratogenicity study of Borriston Labs (1983). The chronic human MED was derived by multiplying the experimental oral dose (560 mg/kg/day), administered on days 7-14 of gestation, by the cube root of the ratio of animal to human body weight, assumed to be $(0.03/70)^{1/3}$, by the weight of a human, assumed to be 70 kg. A human MED of 2955.4747 corresponds to an RV_d of 1. The effect of decreased survival in newborns gives an RV_e of 10. The CS, which is the product of the RV_d and the RV_e, is 10. The corresponding RQ is 1000, as indicated in Table 9-2.

TABLE 9-1

Composite Scores for the Oral Toxicity of Aniline

Species	Dose/Exposure	Chronic Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Mice	560 mg/kg/day days 7-14 of gestation	2955.4747	1	Decreased viability in the pups during the first 3 days of life and perhaps *in utero* as well	10	10	1000	Borriston Labs, 1983
Rats	0.12 aniline in drinking water for 80 weeks (93.6 mg/kg/day)	1120.3764	1	Decreased red blood cell count, hemoglobin levels and hematocrit	4	4	5000	Hagiwara et al., 1980
Rats	3000 ppm dietary aniline hydrochloride (108.2 mg/kg/day)	1295.136	1	Increased hemosiderosis in males and females in both the liver and kidneys.	4	4	5000	NCI, 1978
Rats	6000 ppm dietary aniline hydrochloride (216.4 mg/kg/day)	2590.2719	1	Decreased body weight gain in males and females.	4	4	5000	NCI, 1978
Mice	12,000 ppm dietary aniline hydrochloride (1560 mg/kg/day)	8233.1082	1	Decreased body weight gain in males, but not females	4	4	5000	NCI, 1978

TABLE 9-2

Aniline

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	2955.47 mg/day
Effect:	decreased survival in newborns
Reference:	Borriston Labs, 1983
RV_d:	1
RV_e:	10
Composite Score:	10
RQ:	1000

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*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

As indicated in Table 9-3, the unadjusted $1/ED_{10}$ equals 3.26×10^{-2}. The potency factor (F) of 1.9×10^{-1} was obtained by multiplying the unadjusted $1/ED_{10}$ by the cube root of the ratio of human to animal body weight (70/0.35).

According to IARC (1982), there is "limited evidence" for the carcinogenicity of aniline in experimental animals. Epidemiological data on the carcinogenicity of aniline in humans are insufficient, and IARC (1982) has categorized aniline as a group 3 chemical meaning that while there may be limited carcinogenicity data, overall the data are inadequate to access the human carcinogenic potential. Based on U.S. EPA (1984) guidelines, aniline can be classified as group C, a possible human carcinogen.

TABLE 9-3

Derivation of Potency Factor (F)
Agent: Aniline (given as aniline hydrochloride)

Reference:	NCI, 1978
Exposure route:	oral
Species:	rat
Strain:	Fischer 344
Sex:	male
Vehicle or physical state:	dietary
Body weight:	0.35 kg(reported)
Duration of treatment:	721 days
Duration of study:	753 (749-756) days
Lifespan of animal:	753 (749-756) days
Target organ:	spleen
Tumor type:	hemangiosarcoma
Experimental doses/exposure: (ppm)	2163.6 (3000 ppm aniline hydrochloride) 4327.3 (6000 ppm aniline hydrochloride)
Transformed doses (mg/kg/day):	0, 103.53 and 207.17
Tumor incidence:	0/25, 19/50 and 20/46, respectively
Unadjusted $^1/ED_{10}$:	3.26×10^{-2}
F (potency factor):	1.9×10^{-1}

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. NTIS PB-269605.

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